American Journal of Medical Genetics (Neuropsychiatric Genetics) 67:179–190 (1996)

Irish Study of High-Density Schizophrenia Families: Field Methods and Power to Detect Linkage

Kenneth S. Kendler, F. Anthony O'Neill, John Burke, Bernadette Murphy, Fiona Duke, Richard E. Straub, Rosemary Shinkwin, Mairin Ni Nuallain, Charles J. MacLean, and Dermot Walsh

Departments of Psychiatry (K.S.K., R.E.S., C.J.M.) and Human Genetics (K.S.K., C.J.M.), Medical College of Virginia, Virginia Commonwealth University, Richmond, Virginia; the Department of Psychiatry, Queens University, Belfast, Northern Ireland (F.A.O., F.D.); and Health Research Board, Dublin, Ireland (J.B., B.M., R.S., M.N.N., D.W.)

Large samples of multiplex pedigrees will probably be needed to detect susceptibility loci for schizophrenia by linkage analysis. Standardized ascertainment of such pedigrees from culturally and ethnically homogeneous populations may improve the probability of detection and replication of linkage.

The Irish Study of High-Density Schizophrenia Families (ISHDSF) was formed from standardized ascertainment of multiplex schizophrenia families in 39 psychiatric facilities covering over 90% of the population in Ireland and Northern Ireland. We here describe a *phenotypic* sample and a subset thereof, the *linkage* sample. *Individuals* were included in the phenotypic sample if adequate diagnostic information, based on personal interview and/or hospital record, was available. Only individuals with available DNA were included in the linkage sample. Inclusion of a *pedigree* into the phenotypic sample required at least two first, second, or third degree relatives with nonaffective psychosis (NAP), one of whom had schizophrenia (S) or poor-outcome schizoaffective disorder (PO-SAD). Entry into the linkage sample required DNA samples on at least two individuals with NAP, of whom at least one had S or PO-SAD. Affection was defined by narrow, intermediate, and broad criteria.

The phenotypic sample contained 277 pedigrees and 1,770 individuals and the linkage sample 265 pedigrees and 1,408 individuals. Using the intermediate definition of affection, the phenotypic sample contained 837 affected individuals and 526 affected sibling pairs. Parallel figures for the linkage sample were 700 and 420. Individuals with schizophrenia from these multiplex pedigrees resembled epidemiologically sampled cases with respect to age at onset, gender distribution, and most clinical symptoms, although they were more thought-disordered and had a poorer outcome. Power analyses based on the model of linkage heterogeneity indicated that the ISHDSF should be able to detect a major locus that influences susceptibility to schizophrenia in as few as 20% of families. Compared to first-degree relatives of epidemiologically sampled schizophrenic probands, first-degree relatives of schizophrenic members from the ISHDSF had a similar risk for schizotypal personality disorder, affective illness, alcoholism, and anxiety disorders.

With sufficient resources, large-scale ascertainment of multiplex schizophrenia pedigrees is feasible, especially in countries with catchmented psychiatric care and stable populations. Although somewhat more severely ill, schizophrenic members of such pedigrees appear to clinically resemble typical schizophrenic patients. Our ascertainment process for multiplex schizophrenia families did not select for excess familial risk for affective illness or alcoholism. With its large sample ascertained in a standardized manner from a relatively homogeneous population, the ISHDSF provides considerable power to detect susceptibility loci for schizophrenia. © 1996 Wiley-Liss, Inc.

KEY WORDS: multiplex pedigree, susceptibility loci, linkage analysis

Received for publication April 10, 1995; revision received July 18, 1995.

Address reprint requests to Dr. K. Kendler, Department of Psychiatry, Box 980710, MCV, Richmond VA 23298-0710.

Dr. John Burke is now with the Department of Psychiatry, University of Leicester, UK.

INTRODUCTION

Family, twin, and adoption studies provide substantial evidence that genetic factors play a major role in the etiology of schizophrenia [Gottesman and Shields, 1982; Kendler, 1988; Gottesman et al., 1987; Kendler and Diehl, 1993]. However, several lines of evidence suggest that the mode of transmission of schizophrenia is likely to be complex. First, statistical modeling has, in most samples, suggested that the pattern of schizophrenia in families is unlikely to be explained by a single, major mendelian gene [Elston et al., 1978; Tsuang et al., 1982a; Carter and Chung, 1980; O'Rourke et al., 1982; Risch and Baron, 1984; Vogler et al., 1990]. Second, because the concordance rate for schizophrenia in monozygotic twins is far short of 100% [Gottesman and Shields, 1966; Kendler, 1983], genes for this disorder are unlikely to be completely "penetrant." The existence of clinically unaffected individuals with a high genetic liability to schizophrenia (e.g., "non-penetrant cases") is further supported by the substantially increased risk for schizophrenia in the offspring of unaffected members of monozygotic twin pairs discordant for schizophrenia [Gottesman and Bertelsen, 1989]. Third, because both substance abuse [Bell, 1973; Bowers and Swigar, 1983; Tsuang et al., 1982b] and a wide array of medical disorders [Davison, 1983] can produce clinical states that resemble schizophrenia, a proportion of individuals affected with a "schizophrenia" are probably "phenocopies," having a disorder etiologically unrelated to "true" schizophrenia. Finally, schizophrenia is clinically heterogeneous and, compared with classic mendelian genetic disorders, very common. Therefore, it is likely that schizophrenia is genetically heterogeneous, with different "major" genes influencing liability in different families. Alternatively, the vulnerability to schizophrenia may result from a number of relatively common genes (i.e., "oligogenes"), so that most families with an affected member contain more than one gene which influences the liability to schizophrenia [Suarez et al., 1994].

The detection of linkage for a trait as genetically complex as schizophrenia will probably require large sample sizes [Martinez and Goldin, 1989; Martinez and Goldin, 1990; Kendler and Diehl, 1993; Chen et al., 1992; Levinson, 1993]. Furthermore, standardized rules of ascertainment are likely to be important to improve chances of replication of putative positive results [Cloninger, 1994b].

In anticipation of these issues, we began in 1987 to systematically ascertain and study families in the West of Ireland containing two or more individuals with schizophrenia or poor-outcome schizoaffective disorder (PO-SAD). This project shared instruments, methods, and staff with the Roscommon Family Study (RFS) [Kendler et al., 1993c] which was, for several years, conducted concurrently. Fieldwork in this project, which eventually expanded to include nearly all of Ireland and Northern Ireland, and was therefore named the Irish Study of High-Density Schizophrenia Families (ISHDSF), is now completed. Two preliminary reports from this study have appeared [Su et al., 1993; Pulver et al., 1994]. The present paper has three goals:

1. to describe our ascertainment methods and the sample obtained, including a comparison of the clinical characteristics of the affected members of the high-density pedigrees with those of the epidemiologic sample of probands studied in the RFS;
2. to examine the statistical power of this sample to detect linkage;
3. to estimate the risk for psychiatric disorders in the nonpsychotic relatives of the high-density pedigrees, comparing them with relatives of the schizophrenic probands from the RFS.

METHODS

Sample

The ISHDSF, field work for which was completed between April 1987 and November 1992 in Ireland and November 1988 and November 1992 in Northern Ireland, was sponsored by the Medical College of Virginia; the Health Research Board, Dublin, and the Queen's University, Belfast. Families were ascertained through the public psychiatric hospitals in Ireland and Northern Ireland which, serving catchmented populations, provide over 95% of in-patient psychiatric care. All of these institutions have community nursing services that provide follow-up care for the chronically mentally ill in the community. Because staff turnover is low, the hospital staff, and particularly the community nurses, are quite knowledgeable about patients and their families. In Ireland, where the population is considerably less mobile than in the United States, relatives in a family often live in close proximity to one another.

Ascertainment began with meetings with hospital staff, including psychiatrists, ward nurses, community nurses, and medical record librarians where we would explain the nature and importance of the project. They were asked to provide families that contained two or more individuals who might have psychotic illness. We then obtained and reviewed the available psychiatric records on the affected people in these families. If these records were insufficient to permit a preliminary diagnosis, their caregivers or the individuals themselves were interviewed to obtain further information.

While this informal ascertainment method is efficient, it has two disadvantages. First, we could not determine precisely who in the family was the proband. A mathematical ascertainment correction, as would be needed for complex segregation analysis, would therefore be quite difficult in the ISHDSF. Second, we could not precisely enumerate the number of families referred to us, since different clinicians would refer the same family or parts of the same extended kindred, or withdraw families after deciding that they didn't meet criteria. We estimate that we screened around 1,000 families, but this is only an approximation.

We here present results on two ISHDSF samples: phenotypic and linkage. The phenotypic sample includes all individuals and families meeting entry criteria (see below) on whom we had adequate clinical information. Biological samples were not available on all individuals in the phenotypic sample. Therefore, we also defined a linkage sample which contained those

pedigrees and individuals in the ISHDSF who would be of primary interest for linkage analysis. The linkage sample is entirely a subset of the phenotypic sample.

"Field" Entry Criteria

A series of criteria defined entry for pedigrees and individuals within pedigrees into the ISHDSF. We began with "field" criteria to select those pedigrees that were followed up and exhaustively studied: Two or more first-, second-, or third-degree relatives who, according to the field psychiatrist, met DSM-III-R criteria for schizophrenia or PO-SAD.

No exclusion criteria were used in our selection of families, so that pedigrees were screened neither for bilineal descent of schizophrenia spectrum illness, nor for the presence of other forms of psychopathology, such as bipolar illness. Hodge et al. [1992] has since shown that the actual gain in power from such screening is relatively modest. DSM-III-R schizoaffective disorder was included in these criteria because of earlier evidence from family [Baron et al., 1982; Kendler and Adler, 1984; Kendler et al., 1985, 1986] and adoption studies [Kendler and Gruenberg, 1984; Kendler et al., 1994a] that schizoaffective disorder, when diagnosed by DSM-III-R or similar criteria, has a strong familial/genetic relationship to classic schizophrenia. These results were replicated in the RFS [Kendler et al., 1993c,d; Kendler et al., 1995b]. To be conservative, we excluded from these entry criteria cases who met criteria for DSM-III-R schizoaffective disorder with good inter-episode functioning and/or good outcome on follow-up interview. We did not subtype individuals with schizoaffective disorder cases on the basis of their past history of mania because of the lack of validity of this distinction in the RFS [Kendler et al., 1995a].

We encountered in the ISHDSF 14 individuals with the deteriorating course, negative symptoms, and poor outcome of individuals with classic schizophrenia, but who lacked delusions, hallucinations, or thought disorder. An analysis of individuals with this presentation, previously termed simple schizophrenia, in the RFS [Kendler et al., 1994b], suggested that, from a clinical and familial perspective, they were closely related to classic schizophrenia. Therefore, in the ISHDSF, individuals so diagnosed were considered as meeting entry criteria.

If the family met preliminary screening criteria, we then obtained, from a cooperative family member, a family pedigree from which we decided whom in the family to attempt to interview and sample, using the following rules (where affected means a field diagnosis of schizophrenia or PO-SAD):

1. Sample all affected individuals.
2. Sample all available "connecting" individuals between affected individuals.
3. Sample all available first-degree relatives (age 16 and above) of affected individuals.
4. If a key individual (e.g., parent of a multiplex sibship) is unaffected but cannot be sampled, then attempt to sample up to 3 living siblings.

We then attempted to personally interview all traceable and cooperative family members residing in Ireland, Northern Ireland, or the population centers of England. We also tried to obtain hospital records from all psychiatric hospitalizations. We did not enumerate all eligible relatives, so we cannot calculate a precise cooperation rate. However, our experience was similar to that found in the RFS, where we interviewed 88% of traceable living probands and 86% of traceable, living relatives [Kendler et al., 1993c].

Cooperating Facilities

We approached 32 separate public psychiatric facilities in Ireland and 7 in Northern Ireland. In Ireland, one of these facilities was collaborating with other investigators and so did not participate in our study. Another hospital, serving a new suburban residential area in Dublin with a predominantly young population, was unable to find any families with two psychotic members. The remaining 30 separate psychiatric facilities in Ireland provided us with between 1 to 22 pedigrees that were accepted into the study. The only major psychiatric facilities not approached for participation in the ISHDSF in Ireland were the two private psychiatric hospitals in Dublin. In Northern Ireland, ISHDSF staff approached seven major psychiatric facilities, excluding only those in inner-city Belfast, which provided us between 3 and 17 pedigrees accepted into the study. Of note, 14 pedigrees in the ISHDSF were ascertained in Country Roscommon so that approximately 5% of the ISHDSF sample potentially overlapped with the RFS [Kendler et al., 1993c].

Interviewers, Assessment Methods, and Final Diagnoses

Our field teams consisted of psychiatrists and social scientists with a background in mental health or survey work. Whenever possible, individuals suspected of having psychosis were interviewed by the psychiatrist, with the social scientists interviewing the non-psychotic relatives. All interviewers underwent extensive training by K.S.K. Most members of a high-density pedigree were interviewed by members of the same field team. Thus, interviewers were not routinely blind to the history of psychopathology in relatives.

Our assessment instruments consisted of modified sections of the Structured Interview for DSM-III-R Diagnosis (SCID) [Spitzer et al., 1987] for selected Axis I disorders (major depression, mania, cyclothymia, dysthymia, psychosis, alcohol use, panic disorder, and generalized anxiety disorder) and the Structured Interview for Schizotypy (SIS) for putative schizophrenia spectrum personality disorders (schizotypal, paranoid, schizoid, and avoidant personality disorder) [Kendler et al., 1989]. Where possible, we obtained one or more family history reports from other relatives using the FH-RDC [Endicott et al., 1978] plus family history criteria for schizophrenia related personality disorder [Kendler et al., 1984]. After each interview, interviewers completed a dictation summarizing the results and noting any difficulties with the interview. In 98.6% of cases diagnosed with schizophrenia or schizoaffective

disorder, we were able to obtain psychiatric in-patient and/or out-patient records. A detailed abstract of these records was dictated and a specially developed case record rating scale was completed.

All relevant diagnostic information for each individual relative (SCID, SIS, family history reports, interview dictations, casenote dictations, case record rating scales) was reviewed, blind to pedigree assignment and marker genotype data, independently by K.S.K. and D.W. In this final diagnostic review, a high diagnostic threshold for schizophrenia and schizoaffective disorder was used so that if the available evidence was unclear, a less specific diagnosis was assigned. Each diagnostician made up to three best-estimate DSM-III-R diagnoses, at three levels of certainty: definite, probable, and possible. Disagreements were resolved by consensus. For our 10 diagnostic categories (see below), the two diagnosticians agreed 73.3% of the time. The weighted [Fleiss, 1981] κ value (using weights suggested by Fleiss and Cohen [1973]) was 0.94 ± 0.05.

In addition, one of these raters (K.S.K.), using all available information, assessed, in all cases with nonaffective psychosis, 11 key symptomatic and course variables on the Major Symptoms of Schizophrenia Scale (MSSS): delusions (any), Schneiderian delusions, hallucinations, positive thought disorder (e.g., loosening of association), catatonic symptoms, affective deterioration (e.g., affective flattening), negative thought disorder (e.g., alogia), depressive symptoms, manic symptoms, chronicity of course (from single episode with recovery to chronic course without even partial remissions), and outcome (from full recovery to very poor outcome). These ratings reflected clinical judgment and incorporated the severity of the symptom, its duration, and its relative prominence over the entire course of the illness. While outcome was coded on a 4 point-scale, all other variables were coded on 5 point scales with the following guidelines (details available on request): 1—clearly not present, 2—possibly present but subthreshold, 3—clearly present but moderate, 4—clearly present and prominent, 5—clearly present and severe. Interrater reliability of the MSSS was tested on 47 cases with psychotic illness from the RFS rated blindly by K.S.K. and A. Gruenberg, M.D. Intraclass correlations ranged from + 0.60 for catatonic symptoms to + 0.91 for manic symptoms with a mean (±SD) of + 0.77 ± 0.11.

Diagnostic Categories and Final Inclusion Criteria

In this report, we include only relatives who were assessed by personal interview and/or hospital record and for whom the overall quality of the clinical material was judged sufficient. Although the ISHDSF contains a large number of relatives on whom only family history information is available, these relatives are *not* included in analyses presented here.

For use in subsequent phenotypic and linkage analyses, we constructed a diagnostic hierarchy of 10 categories (outlined in Table 1), which attempted to reflect the probable genetic relationship of these syndromes to definite or classic schizophrenia. The placement of specific disorders in each of the individual categories in this hierarchy were influenced both by previous twin, family, and adoption studies of schizophrenia [Kendler and Diehl, 1993], but especially by the results of the RFS [Kendler et al., 1993a–d, 1994b] (including empirical conformation of the schizophrenia spectrum using a diagnostic hierarchy similar to that proposed here [Kendler et al., 1995b]), conducted in parallel with the ISHDSF in a rural county in the west of Ireland. This hierarchy is similar to that proposed at a workshop on linkage in schizophrenia [Weeks et al., 1990]. We defined three main definitions of affection:

1. Narrow: categories D1 and D2, which we conceptualize to equal "core schizophrenic phenotypes," that is, schizophrenia, PO-SAD, and simple schizophrenia.
2. Intermediate: categories D1 through D5, which we conceptualize as a narrow definition of the schizophrenia spectrum including disorders which have been repeatedly shown to co-aggregate in families with narrowly defined schizophrenia. This category adds to the narrow definition schizotypal personality disorder, and all other nonaffective psychotic disorders (i.e., schizo-

TABLE I. Diagnostic Hierarchy and Number in Each Category for the Phenotypic and Linkage Samples

	Phenotypic		Linkage		
Code	N	%	N	%	Diagnostic categories after DSM-III-R
D1	517	29.2	475	33.7	Definite or probable typical schizophrenia (i.e., hebephrenic, catatonic, paranoid, residual or undifferentiated subtype)
D2	141	8.0	102	7.2	Definite or probable simple schizophrenia or poor outcome schizoaffective disorder or possible typical schizophrenia
D3	25	1.4	18	1.3	Definite or probable schizotypal personality disorder
D4	39	2.2	28	2.0	Possible simple schizophrenia, poor outcome schizoaffective disorder or schizotypal personality disorder or definite, probable or possible nonrecovered schizophreniform disorder
D5	115	6.5	77	5.5	Definite, probable or possible recovered schizophreniform disorder, delusional disorder, atypical psychosis or good outcome schizoaffective disorder
D6	35	2.0	23	1.6	Definite, probable or possible mood incongruent psychotic affective illness
D7	17	1.0	11	0.8	Definite, probable or possible paranoid, avoidant or schizoid personality disorder
D8	36	2.0	20	1.4	Definite, probable or possible mood congruent psychotic affective illness
D9	281	15.9	207	14.7	Any other psychiatric disorder not listed above
D0	564	31.9	447	31.7	No psychiatric disorders

phreniform disorder, delusional disorder, atypical psychosis, and good-outcome SAD).

3. Broad: categories D1–D8, which we conceptualize as a broad definition of the schizophrenia spectrum and includes all disorders which significantly aggregated in relatives of schizophrenic probands in the RFS. This category adds to the intermediate definition mood incongruent and mood congruent psychotic affective illness, and paranoid, avoidant, and schizoid personality disorder.

Final diagnoses sometimes disagreed with field diagnoses, almost always in the more conservative direction. Final inclusion criteria for pedigrees in the ISHDSF was, therefore, based on final diagnoses and required two or more first-, second-, or third-degree relatives with a diagnosis of D1–D5, one or more of whom had a D1 or D2 diagnosis.

This criterion excluded two pedigrees from the sample. Inclusion criteria for families for the linkage subsample of the ISHDSF required that DNA samples be available on two or more first-, second-, or third-degree relatives with a diagnosis of D1–D5, one or more of whom had a D1 or D2 diagnosis. Within families, only individuals with DNA were included in the linkage subsample.

Finally, because we have already typed a large number of polymorphic markers on our linkage subsample, using these genotypes as forensic evidence, we were able to classify relatives into 3 categories on the basis of these genotypes: i) related to other family members as expected, ii) related to other family members, but not as expected (e.g., sample mix-up within families or non-paternity), and iii) not related to other individuals within the pedigree (presumed sample mix-up across families). These methods will be described in detail elsewhere (MacLean et al., in preparation).

General Statistical Methods

To compare characteristics of schizophrenic probands from the ISHDSF and the RFS, we used t-tests for continuous variables and the Kruskal-Wallis test for the ordinal symptom data [SAS Institute, 1990]. To compare the risk of psychiatric illness in the first-degree relatives of schizophrenic individuals from the ISHDSF versus the Roscommon Family Study, we began by selecting, at random, when available, one individual with a final project diagnosis of classical schizophrenia from each high-density family. We then examined all siblings, parents, and offspring of that individual, considering, in both studies, only relatives with a personal interview and/or hospital record. As noted above, proband status could not be unequivocally determined in the ISHDSF. Therefore, we took the conservative approach of defining a "relative" as a member of a high-density pedigree who did not receive a final diagnosis of nonaffective psychosis. We applied a similar approach in the Roscommon Family Study, censoring from our analyses any relative with a diagnosis of nonaffective psychosis. Thus, our analyses were restricted to the following major diagnostic categories: schizotypal personality disorder, affective illness, anxiety disorders (defined as generalized anxiety or panic disorder), and alcoholism (defined as alcohol abuse or dependence). For schizotypal personality disorder, which has no clear age at onset, we compared the prevalence rate in relatives of the high-density and family studies using logistic regression, controlling for gender of relative, age, and relationship of relative to proband (i.e., parent, sibling, or offspring). For the remaining disorders, we utilized a Cox Proportional Hazard model, as implemented in SAS [SAS Institute, 1990], controlling for gender of relative and relationship to proband.

Power Analyses

The goal of power analyses was, assuming a specific genetic model, to estimate the probability of detection of a susceptibility locus for schizophrenia in the ISHDSF if one existed. While many possible genetic models could be used, we have, in accord with most prior studies of this issue [Martinez and Goldin, 1989, 1990; Kendler and Diehl, 1993; Chen et al., 1992; Levinson, 1993], assumed single major locus transmission with inter-pedigree heterogeneity. The genetic parameters have been outlined previously [Su et al., 1993] and appear in the legend of Table V. Marker polymorphism information content (PIC) was assumed to be 0.75.

We varied the proportion of families in which the susceptibility locus was segregating from 5 to 100%. For each data point, we performed 100 stochastic simulations on the entire ISHDSF linkage sample using the program SIMLINK [Boehnke, 1986; Ploughman and Boehnke, 1989], which took approximately 7 hours of central processing unit (CPU) time on a VAX 6620. Results were analyzed in several different ways. We here present findings using the "heterogeneity" or "admixture" LOD score, developed by Smith [1963] and Ott [1983] which jointly estimates evidence for linkage and evidence for linkage heterogeneity. These results were calculated by the program MENDEL [Lange et al., 1988]. Because calculation of this LOD score entails the estimation of an additional parameter (the proportion of "linked families" or α), a LOD score value of 3.7 [Risch, 1989] is equivalent to a LOD of 3 with the standard linkage test [Morton, 1955]. Results were also analyzed by the C-test for linkage heterogeneity [MacLean et al., 1992].

From the 100 simulations, we directly obtained the estimated maximum lod score (or E-LOD), at any value of θ, for that model in the linkage sample of the ISHDSF. That is, we analyzed the simulated data under the same genetic model under which it was generated. In addition, results from these simulations were fit to the noncentral χ^2 distribution [Haynam et al., 1970] to estimate power to detect a LOD score ≥ 3.7. We simulated results for two values of θ between the marker and the putative susceptibility locus: zero and 10%. A 10% recombination rate represents a "worst case scenario" that might occur with a "first-pass" genome scan in which markers were spaced at 20 cM intervals. As we will perform follow-up typing in any region with positive LODs, thereby obtaining "flanking" markers on either side of the putative susceptibility locus, our power will eventually closely approximate that found assuming zero recombination. In fact, with multiple markers, we would eventually

be able to make nearly every family informative, thereby approximating a marker with a PIC value of unity. Since E-LODs and PIC scores are related in a linear fashion, this would produce an approximate 33% gain in the E-LOD value.

RESULTS

"Phenotypic" Sample

Two-hundred seventy-seven pedigrees met entry criteria for inclusion in the "phenotypic" ISHDSF. These pedigrees contained a total of 1,770 individuals with adequate diagnostic information and their distribution by diagnostic class is seen in Table I. Of these 1,770 individuals, personal interviews were available on 1,592 (89.9%), hospital records on 969 (54.8%), and one or more family history reports on 801 (45.3%). A total of 658 relatives (37.2%) met criteria for our *narrow* diagnostic definition (categories D1 or D2), 837 (47.3%) for our *intermediate* diagnostic definition (D1–D5), and 925 (52.3%) for *broad* definition (D1–D8).

The total number of evaluated individuals per pedigree ranged from 2 to 28, with a mean (±SD) of 6.4 ± 3.8. Sixty-eight families (25%) contained only 2 or 3 evaluated individuals, whereas 63 (23%) contained 9 or more evaluated individuals.

The number of affected relatives in individual pedigrees, by the three diagnostic definitions, are seen in Table II. Using the narrow diagnostic definition, 139 families (50.2%) contained two affected individuals and 102 (36.8%) three or more. If the intermediate and broad definitions are used, these numbers become 119 (43.0%) and 158 (57.0%), and 100 (36.1%) and 177 (63.9%), respectively.

Another way of describing this "phenotypic" sample is to enumerate the number of pairs of affected relatives by class of relationship and diagnostic definition (Table III). We count all pairs, so the same individual can contribute to more than one. Of the common relationships examined, the most frequent was affected sibling pairs followed by affected avuncular pairs.

Linkage Sample

Two-hundred sixty-five pedigrees met our criteria for inclusion in the linkage sample. These pedigrees contained 1,408 individuals with adequate clinical information and a DNA sample. In addition, DNA was available on 6 individuals in these families for whom adequate clinical information was lacking. The distribution of these 1,408 individuals, who constitute the linkage sample, by diagnostic category, is seen in Table I and the number of pedigrees by number of affected individuals in Table II. Of the total 265 pedigrees in the linkage sample, using the narrow, intermediate, and broad definitions of illness, 68 (25.7%), 113 (42.6%), 133 (50.2%), respectively, contained 3 or more affected individuals. The number of total pairs of affected relatives, by definition of affection, is seen in Table III. Of note, the linkage sample contained 285, 420, and 505 affected sibling pairs using, respectively, the narrow, intermediate, and broad definitions of illness.

Characteristics of Individuals With Schizophrenia in the ISHDSF

The ISHDSF phenotypic sample contained 581 individuals with a diagnosis of schizophrenia by DSM-III-R. It is of interest to compare the characteristics of these individuals, ascertained through multiplex families from all over Ireland, with the epidemiologic sample of schizophrenic probands ascertained from the Roscommon Case Register. The validity of this comparison is enhanced by the fact that these two patient cohorts were assessed using similar diagnostic instruments by a common research team and diagnosed by the same clinicians.

As seen in Table IV, the gender composition and age at onset of schizophrenic relatives from the ISHDSF were very similar to that found in the Roscommon Family Study. Age at evaluation was significantly older in the ISHDSF. This might be due in part to the restriction in the RFS, but not in the ISHDSF, that probands be born after 1929. Using the MSSS, we compared the intensity of psychotic symptoms over the entire course of illness in the two cohorts. Of the 9 symptoms examined, 2 differences were detected—levels of thought disorder were significantly greater and symptoms of depression significantly less in schizophrenics from multiplex families than from systematically sampled schizophrenic patients. However, global ratings showed that

TABLE II. Number of Pedigrees by Number of Affected Individuals per Pedigree in the Phenotypic and Linkage Samples for Three Definitions of Affection

Number affected	Phenotypic sample Diagnostic definition			Linkage sample diagnostic definition		
	Narrow	Intermediate	Broad	Narrow	Intermediate	Broad
1	36	—	—	38	—	—
2	139	119	100	159	152	132
3	75	81	77	57	72	75
4	20	45	44	7	30	39
5	6	22	35	3	9	12
6		9	15		1	3
7			1	1		3
8			4			
9	1				1	
10						1
12		1				
14			1			

TABLE III. Number of Total Pairs of Affected Relatives by Class of Relationship and Definition of Affection for the Phenotypic and Linkage Samples*

	Phenotypic sample diagnostic definition			Linkage sample diagnostic definition		
Relationship	Narrow	Intermediate	Broad	Narrow	Intermediate	Broad
Full sibling	336	526	650	285	420	505
Parent-offspring	30	109	160	16	54	74
Half-sibling	9	13	22	8	11	18
Avuncular	88	169	208	50	88	105
First cousin	49	97	136	30	54	75
Total	512	914	1,176	389	627	777

*Individual relatives can contribute to more than one pair, so these are not statistically independent.

affected members of multiplex families had a more chronic course and a poorer overall outcome than did epidemiologically sampled cases.

Power Analyses

Assuming that a proportion of the families in the *linkage* sample of the ISHDSF are segregating a major susceptibility locus for schizophrenia, we examined our ability to detect such a locus by stochastic simulations as a function of the percent of pedigrees in which that locus is segregating. We utilize two different statistical methods (presented in Tables V and VI respectively): the standard test for linkage in the presence of heterogeneity [Smith, 1963; Ott, 1983] and the C-test [MacLean et al., 1992].

The first set of results (Table V, lines 1–6) assumes dominant transmission and intermediate diagnostic criteria. Under these assumptions, if a major susceptibility locus for schizophrenia is segregating in 50% or more of the pedigrees in the ISHDSF, we will detect it with near certainty. By contrast, if the most common major locus occurs in 20% or fewer of the families, our chances of detection are slim. Power is still relatively good (67% at $\theta = 0$ for LOD ≥ 3.7) when only 30% of the families are linked.

Since these simulations suggest that the critical range of heterogeneity is around 30%, we assumed this level of heterogeneity in two further sets of simulations. First, we examined the impact of changing diagnostic definition (Table V, lines 7,8), finding that power to detect linkage decreased with a narrow definition and increased with a broad definition of illness. Second, we examined the impact of changing the genetic model (Table V, lines 9–11). Compared to the dominant model, additive models resulted in a moderate loss and the recessive model a moderate gain in power to detect linkage.

We also explored our power to detect linkage using the C-test in simulations which were restricted to the intermediate diagnostic model and dominant transmission (Table VI). Consistent with previous findings that the C-test is superior to the heterogeneity LOD score for samples such as the ISHDSF [MacLean et al.,

TABLE IV. Demographic and Clinical Characteristics of Schizophrenic Relatives From the ISHDSF and Schizophrenic Probands From the Roscommon Family Study

	ISHDSF	Roscommon Family Study	Statistical comparison	P value
Variable N	581	126		
Gender (% male)	67.5%	68.3%	0.03[a]	0.86
Age at onset	24.7 ± 8.0	25.7 ± 7.3	1.26[b]	0.21
Age at evaluation	45.9 ± 14.8	41.8 ± 10.6	3.61[c]	0.0004
Psychotic symptoms over course of illness[e]				
Hallucinations	3.2 ± 1.1	3.2 ± 1.2	0.61[d]	0.43
Delusions, any	3.7 ± 0.9	3.6 ± 1.0	0.48[d]	0.49
Delusions, Schneiderian	2.2 ± 1.1	2.4 ± 1.3	0.76[d]	0.38
Positive thought disorder	2.3 ± 1.0	2.1 ± 1.2	8.63[d]	0.003
Catatonic symptoms	1.5 ± 0.8	1.4 ± 0.8	0.20[d]	0.65
Affective deterioration	3.4 ± 0.9	3.3 ± 1.0	1.99[d]	0.16
Negative thought disorder	2.1 ± 1.1	2.3 ± 1.2	1.43[d]	0.23
Depressive symptoms	1.5 ± 0.7	1.7 ± 0.8	8.77[d]	0.003
Manic symptoms	1.3 ± 0.6	1.2 ± 0.4	0.33[d]	0.56
Course	3.6 ± 0.7	3.4 ± 0.8	10.64[d]	0.001
Outcome	3.0 ± 0.7	2.8 ± 0.8	7.66[d]	0.006

[a] χ^2.
[b] t test—704 df.
[c] t test with unequal variance—240.3 df.
[d] Kruskal-Wallis χ^2 approximation.
[e] Scored on 5-point scale.

TABLE V. Power to Detect Linkage in the ISHDSF Linkage Sample Using the Heterogeneity LOD Score Method

Genetic model	Diagnostic model	Proportion families linked	Mean estimated LOD score (E-LOD)		Proportion of Replicates with LOD ≥							
					2.0		3.0		3.7		5.0	
			θ = 0	θ = .10	θ = 0	θ = .10	θ = 0	θ = .10	θ = 0	θ = .10	θ = 0	θ = .10
Dom	Int	.10	1.12	0.77	.16	.12	.10	.04	.07	.02	.02	.00
Dom	Int	.20	2.75	1.22	.56	.21	.38	.11	.29	.08	.15	.01
Dom	Int	.30	5.35	2.44	.84	.48	.73	.26	.67	.20	.46	.13
Dom	Int	.50	13.39	5.46	1.00	.86	1.00	.84	1.00	.74	.97	.56
Dom	Int	.75	27.94	10.96	1.00	.99	1.00	.98	1.00	.96	1.00	.93
Dom	Int	1.00	49.32	18.72	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Dom	Narrow	.30	3.04	1.42	.70	.27	.48	.19	.35	.11	.20	.02
Dom	Broad	.30	6.54	3.17	.93	.66	.83	.46	.75	.33	.63	.19
Add-P	Int	.30	3.46	2.20	.67	.40	.52	.26	.41	.19	.21	.12
Add-L	Int	.30	2.86	1.06	.63	.18	.44	.07	.31	.04	.15	.01
Rec	Int	.30	7.25	3.01	.98	.56	.92	.40	.84	.32	.74	.21

θ, recombination fraction; Dom, indicates dominant; Int, intermediate; Add-P, additive on the penetrance scale; Add-L, additive on the liability scale; Rec, recessive. For the narrow, intermediate and broad diagnostic definitions, we assume lifetime risks of 0.6, 3.0, and 4.0%, respectively. The figures are similar to those obtained in relatives of controls from the Roscommon Family Study [Kendler et al., 1993c]. Penetrances were estimated and gene frequencies were set to produce phenocopy rates of 10%, 20% and 25% for the narrow, intermediate, and broad diagnostic definitions. For the intermediate dominant model, the schizophrenia gene frequency and the penetrances were .0161, .75, .75, and .0062, respectively. For the narrow dominant model, these figures were .0049, .55,.55, and .0006, respectively. For the broad dominant model, these figures were .0178, .85, .85, and .0104, respectively. For the intermediate additive-penetrance model, these figures were .032, .75, .375, and .0064, respectively. For the intermediate additive-liability model, these figures were .0614, .75, .185, and .0068, respectively. For the intermediate recessive model, these figures were .1789, .75, .0062, and .0062, respectively.

1992], we found with the C-test that we had considerable power, even with the rigorous level of $P \leq 0.0001$, to detect linkage when only 20% of the families had a linked gene.

Risk for Non-Schizophrenia Spectrum Disorders in Relatives

In ascertaining multiplex schizophrenia pedigrees, were we selecting for a familial vulnerability to disorders other than schizophrenia or related spectrum conditions? To address this question, we compared, by a Cox proportional hazard model, the risk for various psychiatric disorders in the first-degree relatives (excluding those with nonaffective psychosis) of schizophrenic individuals from the phenotypic sample of the ISHDSF (n = 556) with that found in the first-degree relatives of the epidemiologically sampled schizophrenic probands from the RFS (n = 320).

Compared to the relatives of schizophrenic probands from the Roscommon study, relatives of schizophrenic patients from the ISHDSF had a *higher* risk for bipolar illness (all df = 1) (odds ratio [OR] = 1.80, $P = 0.24$), total affective illness (OR = 1.06, $P = 0.68$) and anxiety disorder (OR = 1.44, $P = 0.16$) and a *lower* risk for major depression (OR = 0.97, $P = 0.88$) and alcoholism (OR = 0.83, $P = 0.40$). However, none of these differences approached statistical significance. By logistic regression, the prevalence of schizotypal personality disorder also did not significantly differ in the two relative groups (OR = 0.69, df = 0.23).

COMMENT

Ascertainment Methods and Sample Obtained

Our results suggest that it is feasible to conduct, using standardized techniques, hospital-based ascertainment for multiplex schizophrenia pedigrees in a large geographical area. Four factors were central to our success. First, family structure is relatively intact in Ireland, with most family members residing in close geographical proximity to one another. Second, psychiatric care in both Ireland and Northern Ireland is catchmented—so that affected members of families were likely to be treated in the same facility. Third, the medical and nursing staff of most psychiatric facilities in

TABLE VI. Proportion of Replicates With Power to Detect Linkage in the ISHDSF Sample Using the C-Test*

Proportion of families linked	$P \leq .01$		$P \leq .001$		$P \leq .0001$		$P \leq .00001$	
	θ = 0	θ = .10	θ = 0	θ = .10	θ = 0	θ = .10	θ = 0	θ = .10
.10	.29	.11	.10	.03	.03	.00	.00	.00
.20	.84	.40	.63	.17	.42	.06	.23	.02
.30	.99	.75	.96	.49	.89	.28	.77	.13
.50	1.00	.99	1.00	.95	1.00	.88	1.00	.75
.75	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00

*Assuming dominant transmission and the intermediate diagnostic definition.

Ireland and Northern Ireland have a low turnover, individuals who have worked for 2 decades in the same hospital being relatively common. Therefore, many of these professionals had "long memories," allowing them to recall affected relatives who may have been admitted many years apart. Fourth, nearly all psychiatric facilities in Ireland and Northern Ireland have active out-reach services that provide supportive care and pharmacotherapy for individuals with chronic psychotic illness in the community. Most of these community nurses know well both the patients and their relatives and were a great source of referrals for potential multiplex families.

However, we also understood the limitations of this method. Our ascertainment was not systematic, as might have been accomplished by studying the family of every treated schizophrenic patient in Ireland and Northern Ireland. It is nearly certain, therefore, that our ascertainment process was neither complete nor free of bias. The number of families we successfully ascertained differed widely across different institutions, and this discrepancy could not be easily explained by differences in the population of the catchment area. While true differences in the frequency of multiplex schizophrenia families across populations might explain these differences, it was our impression that other factors also influenced the success of our efforts. Not surprisingly, the cooperation and enthusiasm of the medical and nursing staff appeared to be important. Urbanization also seemed to have a negative effect on our ability to ascertain multiplex pedigrees. We suspect that this was due to several factors, including smaller average family size, greater disruption of the family structure (so ill individuals were less likely to be treated in the same facility), less stability of staff in "inner-city" psychiatric services and poorer staff knowledge of the family background of their patients. Finally, our ability to efficiently ascertain multiplex pedigrees in this manner was highly dependent on the availability and quality of psychiatric records. Although on average of good quality, we did encounter psychiatric facilities where our efforts were hampered by records that were difficult to find or of low quality.

While we are unable to accurately estimate the bias or level of completeness of our ascertainment for multiplex schizophrenia pedigrees, we can, with greater confidence, examine the characteristics of the schizophrenic family members whom we did ascertain. We can do this because we have previously studied an epidemiologic sample of treated schizophrenic probands in county Roscommon, Ireland. The ISHDSF and RFS were conducted in parallel, with similar assessment instruments, shared staff, and the same senior diagnostician (K.S.K.).

Schizophrenic family members from the ISHDSF closely resembled the epidemiologic sample of schizophrenic probands from the RFS [Kendler et al., 1993c] with respect to gender composition, age at onset, and prominence of most major schizophrenic symptoms, including delusions, hallucinations, and negative symptoms. Only levels of thought disorder and depression distinguished the two groups and even here the differences were modest. These results suggest that in Ireland, from a clinical and demographic perspective, "typical" and "familial" schizophrenia appear to be similar. Our results do not support previous suggestions that familial schizophrenia is characterized by an early age at onset [Kendler et al., 1987; Kendler and MacLean, 1990; Pulver et al., 1990; Albus et al., 1994; Walsh et al., 1993] or a preponderance of females [Goldstein et al., 1990; Wolyniec et al., 1992; Maier et al., 1993].

However, schizophrenic individuals in the ISHDSF did display a significantly more chronic course and poorer outcome than schizophrenic probands from the Roscommon Family study. This might reflect a real difference, suggesting, contrary to most previous evidence [Kendler and Tsuang, 1988] including from the RFS [Kendler et al., 1994c], that "familial" schizophrenia tends toward a particularly malignant course. Alternatively, the difference could result from the different ascertainment strategies in the RFS and ISHDSF. In the RFS, ascertainment required only a single in- or outpatient psychiatric contact. In the ISHDSF, ascertainment occurred when mental health providers recalled that individuals belonged to multiplex kindreds. Since schizophrenic individuals with chronic illness are likely to be in frequent contact with care-givers, poorer outcome cases of schizophrenia may simply have been easier for referring physicians to recall.

Power to Detect Linkage

Containing 265 small to medium sized pedigrees, the ISHDSF linkage sample provides substantial power to detect susceptibility loci for schizophrenia. Our simulations suggested that we would have a high probability of detecting a gene of major effect for schizophrenia if it were present in as few as 20% or more of families. If, by contrast, the most common major gene for schizophrenia were present in much fewer than 20% of pedigrees, our chances of detection in the ISHDSF would be slim. Our power simulations are broadly consistent with previous analyses [Martinez and Goldin, 1989, 1990; Kendler and Diehl, 1993; Chen et al., 1992; Levinson, 1993] in suggesting that 200 or more small to medium sized pedigrees are needed to detect reliably linkage in complex disorders with substantial genetic heterogeneity. Our results are also supportive of previous studies in suggesting that if the most common major gene is present in one-fifth or fewer of high-density pedigrees, detection by linkage analysis will be very difficult with realistic sample sizes.

Our power analyses, however, have not been exhaustive. In particular, we have examined only locus heterogeneity—various distinct and relatively rare "major genes" each acting in different pedigrees. We did not here consider the equally plausible, although statistically more complex, scenario that schizophrenia is due to two or more relatively common loci—several of which are typically segregating in high-density families [Suarez et al., 1994]. Furthermore, we have not addressed the important problem of discriminating false from true positives when many markers are tested in a genome-wide scan [Lander and Schork, 1994].

In addition to its size, two other characteristics of the ISHDSF may increase its power to detect linkage for

schizophrenia. First, while not a genetic isolate, Ireland is, compared either to the United States or Continental Europe as a whole, less genetically heterogeneous [Relethford, 1983; Sunderland et al., 1973; Cavalli-Sforza et al., 1994]. If susceptibility loci for schizophrenia differ across human populations, this variation would probably be lower in Ireland than in many other populations where studies of high-density schizophrenia families are currently ongoing. Second, in contrast to its increasing frequency, particularly in individuals with psychotic illness, in many urban areas in the US and Europe, non-alcohol substance abuse or dependence, especially involving stimulants, cocaine, or psychedelics, is nearly unknown in Ireland and Northern Ireland. Only 4 individuals in the phenotypic ISHDSF sample met criteria, for a lifetime prevalence of 0.2%. Two of these individuals abused sedative-hypnotics, and one each heroin and hashish. In neither of the 2 of these cases which also had psychotic illness did the drug abuse present a problem of differential diagnosis.

Pattern of Psychiatric Disorders in Nonpsychotic Relatives

A major concern in the study of high-density schizophrenia families is the degree to which the process of ascertainment biases the samples obtained. In addition to examining characteristics of the probands themselves, we also examined the pattern of psychiatric illnesses in relatives. In particular, we asked whether the risk for major forms of psychopathology differs between first-degree relatives of i) schizophrenic individuals from our multiplex pedigrees and ii) the epidemiologically sampled schizophrenic probands from the Roscommon Family Study.

Despite substantial sample sizes, we were unable to find significant difference in the rates of major forms of psychopathology in the two groups of relatives. It might at first seem surprising that the rate of schizotypal personality disorder did not differ in these two samples, given prior strong evidence for a familial/genetic relationship between schizophrenia and schizotypal personality disorder [Kendler and Diehl, 1993; Kendler et al., 1993b]. However, there are two plausible a priori hypotheses that predict opposite results. Because relatives from the ISHDSF on average had a higher familial liability to schizophrenia, they should be more prone to schizotypal personality disorder However, multiplex families may be selected because, for either genetic or environmental reasons, they have a "high penetrance" for the schizophrenic genotype. That is, individuals with a genetic susceptibility may, in such families, be particularly prone to develop classic schizophrenic illness, leaving few to manifest the milder schizophrenia-spectrum personality disorders.

We also found no significantly increased risk for bipolar or unipolar affective illness in the relatives of our multiplex versus epidemiologically sampled schizophrenic probands. These results suggest that, despite our inclusion of PO-SAD as a "core" phenotype, our ascertainment procedure did not substantially oversample individuals or families with a high vulnerability to affective illness. Since bipolar illness is so familial [Tsuang and Faraone, 1990], if, due to misdiagnosis, even a modest proportion of our core schizophrenic and schizoaffective disorder relatives "truly" had bipolar illness, we should have seen a significantly higher rate of affective illness in relatives. Furthermore, these results bear on the long-standing question of the familial relationship between schizophrenia and affective illness [Cloninger, 1994a; Crow, 1994; Weissman et al., 1994]. Given that our multiplex families had a higher average familial liability to schizophrenia than our epidemiologic sample, if the genetic susceptibility to schizophrenia and affective illness were substantially correlated we should have observed higher rates of affective illness in the multiplex versus epidemiologic sample. That we did not provides further evidence, consistent with our findings in the RFS [Kendler et al., 1993a], that schizophrenia and affective illness are relatively distinct familial syndromes.

Limitations

Results presented here should be interpreted in the context of three important methodologic limitations. First, while ascertainment efforts in the ISHDSF were well standardized, they were not truly "epidemiologic," relying as they did on mental health professionals to recall and report possible high-density schizophrenia families. Given our sampling, the utility of the ISHDSF to determine the mode of transmission of schizophrenia by complex segregation analysis is limited. Second, interviewers were not kept blind to knowledge about psychopathology in other relatives, although they were repeatedly cautioned to avoid bias in their assessments. The clinical ratings reported here were performed blindly and interviewers and diagnosticians were also blind to marker genotype. However, since the clinical ratings were based on non-blind interviews it is possible, albeit unlikely, that they were also biased. Third, our power analyses were limited and did not attempt to cover all plausible genetic models for schizophrenia.

A large scale effort is now underway to conduct a genome-wide scan for susceptibility genes to schizophrenia in the ISHDSF, utilizing both parametric and nonparametric linkage methods. Preliminary evidence for linkage in the 6p region has been detected [Straub et al., 1995]. The eventual value of the ISHDSF will, to a large extent, depend on the success of this and parallel efforts underway in other laboratories to detect and replicate, by linkage analysis, susceptibility loci for schizophrenia.

ACKNOWLEDGMENTS

This project was largely supported by grant MH41953 from the United States National Institute of Mental Health (NIMH). Additional support came from NIMH grant MH45390, a Research Scientist Award to K.S.K. (MH01277), the Scottish Rite Benevolent Foundation's Schizophrenia Research Program, Northern Masonic Jurisdiction, U.S.A., the MacDonough Foundation, and the A.D. Williams Foundation. Data collection was conducted under the supervision of Susan Humphries, M.Sc., Mary Healy, M.Sc., and Aine Finnerty,

B.Soc.Sci. Additional interviews were conducted by Fiona McMahon, B.A., Jacinta Downing, M.Soc.Sci, Teresa Hebron, B.A., Bernadine Hanratty, M.Soc.Sci, Eileen Crowe, B.A., Michael Doherty, M.D., Joseph Bray, M.B., and Lesly Lowry, R.N. Administrative support was provided by Laura Tighe, Rita Fleming, Myra Mullaney, Mary O'Brien, B.A., Deirdre Carey, B.A., and John O'Gorman, A.C.I.S.. This project would not have been possible without the cooperation of the families themselves and the staffs of the many psychiatric hospitals and units in Ireland and Northern Ireland and their cooperation is gratefully acknowledged. We also wish to acknowledge the assistance of Kitty Williams, L. Thacker, M.S., S.R. Diehl, Ph.D., L. Karkowski-Shuman, Ph.D., B. Duke, M.S., R. McClelland, M.D., M. McGuire M.B., A. O'Hare, M.Soc.Sci., and M.P. Spellman, M.B.

REFERENCES

Albus M, Scherer J, Hueber S, Lechleuthner T, Kraus G, Zausinger S, Burkes S (1994): The impact of familial loading on gender differences in age at onset of schizophrenia. Acta Psychiatr Scand 89:132–134.

Baron M, Gruen R, Asnis L, Kane J (1982): Schizoaffective illness, schizophrenia and affective disorders: Morbidity risk and genetic transmission. Acta Psychiatr Scand 65:253–262.

Bell DS (1973): The experimental reproduction of amphetamine psychosis. Arch Gen Psychiatry 29:35–40.

Boehnke M (1986): Estimating the power of a proposed linkage study: a practical computer simulation approach. Am J Hum Genet 39:513–527.

Bowers MB Jr, Swigar ME (1983): Vulnerability to psychosis associated with hallucinogen use. Psychiatry Res 9:91–97.

Carter CL, Chung CS (1980): Segregation analysis of schizophrenia under a mixed genetic model. Hum Hered 30:350–356.

Cavalli-Sforza LL, Menozzi P, Piazza A (1994): "The History and Geography of Human Genes." Princeton, NJ: Princeton University Press.

Chen WJ, Faraone SV, Tsuang MT (1992): Linkage studies of schizophrenia: a simulation study of statistical power. Genet Epidemiol 9:123–139.

Cloninger CR (1994a): Pro: Tests of alternative models of the relationship of schizophrenia and affective psychoses. In Gershon ES, Cloninger CR (eds): "Genetic Approaches to Mental Disorders." Washington, DC: American Psychiatric Press, pp 149–162.

Cloninger CR (1994b): Turning point in the design of linkage studies of schizophrenia. Am J Med Genet 54:83–92.

Crow TJ (1994): Con: the demise of the Kraepelinian binary system as a prelude to genetic advance. In Gershon ES, Cloninger CR (eds): "Genetic Approaches to Mental Disorders." Washington, DC: American Psychiatric Press, pp 163–192.

Davison K (1983): Schizophrenia-like psychoses associated with organic cerebral disorders: a review. Psychiatr Dev 1:1–34.

Elston RC, Namboodri KK, Spence MA, Rainer JD (1978): A genetic study of schizophrenia pedigrees. II. One locus hypotheses. Neuropsychobiology 4:193–206.

Endicott J, Andreasen N, Spitzer RL (1978): "Family History Research Diagnostic Criteria." New York: Biometrics Research, New York Psychiatric Institute.

Fleiss J (1981): "Statistical Methods for Rates and Proportions," 2nd ed. New York: John Wiley & Sons.

Fleiss JL, Cohen J (1973): The equivalence of weighted kappa and the intraclass correlation coefficient as measures of reliability. Educ Psychol Meas 33:613–619.

Goldstein JM, Faraone SV, Chen WJ, Tolomiczencko GS, Tsuang MT (1990): Sex differences in the familial transmission of schizophrenia. Br J Psychiatry 156:819–826.

Gottesman II, McGuffin P, Farmer AE (1987): Clinical genetics as clues to the "real" genetics of schizophrenia: (a decade of modest gains while playing for time). Schizophr Bull 13:23–47.

Gottesman II, Bertelsen A (1989): Confirming unexpressed genotypes for schizophrenia: risks in the offspring of Fischer's Danish identical and fraternal discordant twins. Arch Gen Psychiatry 46: 867–872.

Gottesman II, Shields J (1966): Contributions of twin studies to perspectives on schizophrenia. In Maher BA (ed): "Progress in Experimental Personality Research," Vol 3. New York: Academic Press.

Gottesman II, Shields J (1982): "Schizophrenia: The Epigenetic Puzzle." New York: Cambridge University Press.

Haynam GE, Govindarajulu Z, Leone FC (1970): Tables of the cumulative non-central chi-square distribution. In Harter HL, Owen DB (eds): "Selected Tables in Mathematical Statistics," Vol I. Providence, RI: American Mathematical Society, pp 1–78.

Hodge SE (1992): Do bilineal pedigrees represent a problem for linkage analysis? Basic principles and simulation results for single-gene diseases with no heterogeneity. Genet Epidemiol 9: 191–206.

Kendler KS (1983): Overview: A current perspective on twin studies of schizophrenia. Am J Psychiatry 140:1413–1425.

Kendler KS, Masterson C, Ungaro R, Davis K (1984): A family history study of schizophrenia-related personality disorder. Am J Psychiatry 141:424–427.

Kendler KS, Gruenberg AM, Tsuang MT (1985): Psychiatric illness in first-degree relatives of schizophrenic and surgical control patients: A family study using DSM-III criteria. Arch Gen Psychiatry 42: 770–779.

Kendler KS, Gruenberg AM, Tsuang MT (1986): A DSM-III family study of the non-schizophrenic psychotic disorders. Am J Psychiatry 143:1098–1105.

Kendler KS, Tsuang MT, Hays P (1987): Age at onset in schizophrenia: a familial perspective. Arch Gen Psychiatry 44:881–890.

Kendler KS (1988): The genetics of schizophrenia: an overview. In Nasrallah HA (series editor), Tsuang MT, Simpson JC (volume editors) (eds): "Handbook of Schizophrenia. Vol. 3: Nosology, Epidemiology, and Genetics." Amsterdam: Elsevier Science, pp 437–462.

Kendler KS, Lieberman JA, Walsh D (1989): The Structured Interview for Schizotypy (SIS): A preliminary report. Schizophr Bull 15: 559–571.

Kendler KS, McGuire M, Gruenberg AM, O'Hare A, Spellman M, Walsh D (1993a): The Roscommon Family Study. IV: Affective illness, anxiety disorders and alcoholism in relatives. Arch Gen Psychiatry 50:952–960.

Kendler KS, McGuire M, Gruenberg AM, O'Hare A, Spellman M, Walsh D (1993b): The Roscommon Family Study. III: Schizophrenia-related personality disorders in relatives. Arch Gen Psychiatry 50:781–788.

Kendler KS, McGuire M, Gruenberg AM, O'Hare A, Spellman M, Walsh D (1993c): The Roscommon Family Study. I: Methods, diagnosis of probands and risk of schizophrenia in relatives. Arch Gen Psychiatry 50:527–540.

Kendler KS, McGuire M, Gruenberg AM, Spellman M, O'Hare A, Walsh D (1993d): The Roscommon Family Study. II: The risk of nonschizophrenic nonaffective psychoses in relatives. Arch Gen Psychiatry 50:645–652.

Kendler KS, Gruenberg AM, Kinney DK (1994a): Independent diagnoses of adoptees and relatives as defined by DSM-III in the provincial and national samples of the Danish Adoption Study of Schizophrenia. Arch Gen Psychiatry 51:456–468.

Kendler KS, McGuire M, Gruenberg AM, Walsh D (1994b): An epidemiologic, clinical, and family study of simple schizophrenia in County Roscommon, Ireland. Am J Psychiatry 151:27–34.

Kendler KS, McGuire M, Gruenberg AM, Walsh D (1994c): Clinical heterogeneity in schizophrenia and the pattern of psychopathology in relatives: Results from an epidemiologically based family study. Acta Psychiatr Scand 89:294–300.

Kendler KS, McGuire M, Gruenberg AM, Walsh D (1995a): Examining the validity of DSM-III-R schizoaffective disorder and its putative subtypes in the Roscommon Family Study. Am J Psychiatry 152:755–764.

Kendler KS, Neale MC, Walsh D (1995b): Evaluating the spectrum concept of schizophrenia in the Roscommon Family Study. Am J Psychiatry 152:749–754.

Kendler KS, Adler D (1984): The pattern of illness in pairs of psychotic siblings. Am J Psychiatry 141:509–513.

Kendler KS, Diehl SR (1993): The genetics of schizophrenia: a current, genetic-epidemiologic perspective. Schizophr Bull 19:261–285.

Kendler KS, Gruenberg AM (1984): An independent analysis of the Copenhagen sample of the Danish Adoption Study of Schizophrenia. VI: The relationship between psychiatric disorders as defined by DSM-III in the relatives and adoptees. Arch Gen Psychiatry 41:555–564.

Kendler KS, MacLean CJ (1990): Estimating familial effects on age at onset and liability to schizophrenia. I: Results of a large sample family study. Genet Epidemiol 7:409–417.

Kendler KS, Tsuang MT (1988): Outcome and familial psychopathology in schizophrenia. Arch Gen Psychiatry 45:338–346.

Lander ES, Schork NJ (1994): Genetic dissection of complex traits. Science 265:2037–2048.

Lange K, Weeks D, Boehnke M (1988): Programs for pedigree analysis: MENDEL, FISHER, and GENE. Genet Epidemiol 5:471–472.

Levinson DF (1993): Power to detect linkage with heterogeneity in samples of small nuclear families. Am J Med Genet (Neuropsychiatr Genet) 48:94–102.

MacLean CJ, Ploughman LM, Diehl SR, Kendler KS (1992): A new test for linkage in the presence of locus heterogeneity. Am J Hum Genet 50:1259–1266.

Maier W, Lichtermann D, Minges J, Heun R, Hallmayer J (1993): The impact of gender and age at onset on the familial aggregation of schizophrenia. Eur Arch Psychiatry Clin Neurosci 242:279–285.

Martinez MM, Goldin LR (1989): The detection of linkage and heterogeneity in nuclear families for complex disorders: One versus two marker loci. Am J Hum Genet 44:552–559.

Martinez MM, Goldin LR (1990): Power of the linkage test for a heterogeneous disorder due to two independent inherited causes: a simulation study. Genet Epidemiol 7:219–230.

Morton NE (1955): Sequential tests for the detection of linkage. Am J Hum Genet 7:277–318.

O'Rourke DH, Gottesman II, Suarez BK, Rice J, Reich T (1982): Refutation of the general single-locus model for the etiology of schizophrenia. Am J Hum Genet 34:630–649.

Ott J (1983): Linkage analysis and family classification under heterogeneity. Ann Hum Genet 47:311–320.

Ploughman LM, Boehnke M (1989): Estimating the power of a proposed linkage study for a complex genetic trait. Am J Hum Genet 44:543–551.

Pulver AE, Brown CH, Wolyniec P, McGrath J, Tam D, Adler L, Carpenter T, Childs B (1990): Schizophrenia: age on onset, gender and familial risk. Acta Psychiatr Scand 82:344–351.

Pulver AE, Karayiorgou M, Lasseter VK, Wolyniec P, Kasch L, Antonarakis S, Housman D, Hazazian HH, Meyers D, Nestadt G, Ott J, Liang K-Y, Lamacz M, Thomas M, Childs B, Diehl SR, Wang S, Murphy B, Sun C, O'Neill FA, Nie L, Sham P, Burke J, Duke BW, Duke F, Kipps BR, Bray J, Hunt W, Shinkwin R, Ni Nuallain M, Su Y, MacLean CJ, Walsh D, Kendler KS, Gill M, Vallada H, Mant R, Asherson P, Collier D, Parfitt E, Roberts E, Nanko S, Walsh C, Daniels J, Murray R, McGuffin P, Owen M, Laurent C, Dumas J-B, d'Amato T, Jay M, Martinez M, Campion D, Mallet J (1994): Follow-up of a report of a potential linkage for schizophrenia on chromosome 22q12–q13.1: part 2. Am J Med Genet (Neuropsychiatr Genet) 54:44–50.

Relethford JH (1983): Genetic structure and population history of Ireland: A comparison of blood group and anthropometric analyses. Ann Hum Biol 10:321–334.

Risch N (1989): Linkage detection tests under heterogeneity. Genet Epidemiol 6:473–480.

Risch N, Baron M (1984): Segregation analysis of schizophrenia and related disorders. Am J Hum Genet 36:1039–1059.

SAS Institute (1990): "SAS/STAT User's Guide," Version 6, Vols 1 and 2," 4th ed. Cary, NC: SAS Institute Inc.

Smith CAB (1963): Testing for heterogeneity of recombination fraction values in human genetics. Ann Hum Genet 27:175–182.

Spitzer RL, Williams JB, Gibbon M (1987): "Structured Clinical Interview for DSM-III-R." New York: Biometrics Research Dept, New York State Psychiatric Institute.

Straub RE, MacLean CJ, O'Neill FA, Burke J, Murphy B, Duke F, Webb T, Zhang J, Walsh D, Kendler KS (1995): A potential vulnerability locus for schizophrenia on chromosome 6p24-22: evidence for genetic heterogeneity. Nature Genetics, in press.

Su Y, Burke J, O'Neill FA, Murphy B, Nie L, Kipps B, Bray J, Shinkwin R, Ni Nuallain M, MacLean CJ, Walsh D, Diehl SR, Kendler KS (1993): Exclusion of linkage between schizophrenia and the D2 dopamine receptor gene region of chromosome 11q in 112 Irish multiplex families. Arch Gen Psychiatry 50:205–211.

Suarez BK, Hampe CL, Van Eerdewegh P (1994): Problems of replicating linkage claims in psychiatry. In Gershon ES, Cloninger CR (eds): "Genetic Approaches to Mental Disorders." Washington, DC: American Psychiatric Association Press, pp 23–46.

Sunderland E, Tills D, Bouloux C, Doyl J (1973): Genetic studies in Ireland. In Roberts DF, Sunderland E (eds): "Genetic Variation in Britain," Vol XII. London: Taylor & Francis, pp 141–170.

Tsuang MT, Bucher KD, Fleming JA (1982a): Testing the monogenic theory of schizophrenia: an application of segregation analysis to blind family study data. Br J Psychiatry 140:595–599.

Tsuang MT, Simpson JC, Kronfol Z (1982b): Subtypes of drug abuse with psychosis: Demographic characteristics, clinical features, and family history. Arch Gen Psychiatry 39:141–147.

Tsuang MT, Faraone SV (1990): "The Genetics of Mood Disorders." Baltimore: The Johns Hopkins University Press.

Vogler GP, Gottesman II, McGue MK, Rao DC (1990): Mixed model segregation analysis of schizophrenia in the Lindelius Swedish pedigrees. Behav Genet 20:461–472.

Walsh C, Asherson P, Castle D, Sham P, Williams J, Taylor C, Owen M, Gill M, McGuffin P, Murray R (1993): Familial schizophrenia shows no gender difference in age of onset. Schizophr Res 9: 127–128.

Weeks DE, Brzustowicz L, Squires-Wheeler E, Cornblatt B, Lehner T, Stefanovich M, Bassett A, Gilliam TC, Ott J, Erlenmeyer-Kimling L (1990): Report of a workshop on genetic linkage studies in schizophrenia. Schizophr Bull 16:673–686.

Weissman MM, Fink M, Endicott J, Taylor MA, Kendler KS, Winokur G, Gershon ES (1994): Discussion of debate: is there a genetic Kraepelinian dichotomy for manic-depressive illness and schizophrenia? In Gershon ES, Cloninger CR (eds): "Genetic Approaches to Mental Disorders." Washington, DC: American Psychiatric Press, pp 193–202.

Wolyniec TS, Pulver AE, McGrath JA, Tam D (1992): Schizophrenia: gender and familial risk. J Psychiat Res 26:17–27.